Perceptual and Motor Skills, 2002, 95, 897-900. © Perceptual and Motor Skills 2002

THE BRAIN MATRIX AND MULTIFOCAL BRAIN DAMAGE FOLLOWING A SINGLE INJECTION OF KETAMINE IN YOUNG ADULT RATS: CONSPICUOUS CHANGES IN OLD AGE[1]

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Summary.—Male rats were seized with lithium and pilocarpine and then injected within 30 min. with either acepromazine or ketamine. These rats as well as age-matched normal rats were observed daily for one year. The rats which had received the ketamine after the seizures were significantly heavier than either the normal rats or the other group of seized rats. The bulk of this increased weight was due to the marked increase in white, extremely dense adipose tissue. Compared to the acepromazine-treated rats, the ketamine-treated rats did not exhibit spontaneous seizures and exhibited cerebral widths comparable to normal rats. These results suggest that the multifocal, graded neuronal loss associated with this seizure model may allow other "configurations" to emerge that can support normal behaviors as well as new characteristics.

The brain can be considered a neuromatrix. Our definition of neuromatrix is a larger space containing very large numbers of smaller spaces in which there are groups of neurons or elements whose functional connections result in emergent properties. These properties are determined by the specific timing of the arrival of neuroelectromagnetic information within the different sets of elements and coherence of this activation over much larger spaces. These functional connections are determined by both the distances between the groups of neurons as well as the time required for their interactions.

One of the properties of a matrix is that alterations in its intrinsic connections or operations result in different properties. Although the pervasive innervations of all organs by nonmyelinated or myelinated axons from the autonomic nervous system would suggest the brain modulates, monitors, or even controls the structural and functional status of organs, we have been pursuing the concept that radical changes in the neuromatrix may result in signals that radically alter the size and potentially the histological composition of organs and the organism.

Subcutaneous injection of clinical dosages of lithium (3 mEq/kg) followed 4 to 24 hr. by 30 mg/kg of a muscarinic agent evokes epileptic seizures. The chemical correlates of these perturbations result in neuronal loss within about 100 Paxinos and Watson structures within the rat brain. The specific

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pattern of damage can be influenced by the type of drug given after the onset of the seizures. Most occurrences of brain damage would not specify the characteristics of this matrix because the spatial extent of the damage would eliminate large numbers of the elements. For example, Boyko, Galabru, McGeer, and McGeer (1979) found that multifocal damage induced by intracerebral injections of kainic acid produced periarteriolar myocardial necrosis.

We also reasoned that these effects should be most evident in older rats whose brains had been changed as young adults because such large durations would be required for the pattern of information from the brain to alter the organs or for any small change, acquired immediately following the injury, to be amplified by normal ontogenetic changes. The argument would be similar to that associated with the detection of an aberrant mitosis in a single cell. Because approximately 40 to 45 doublings, e.g., 2, 4, 8, 16, . . . n, would be required before the aberrant aggregate would approach the volume defined by most organs, latencies of years (in the human) might be required, depending upon mitosis rate, before the effect would become obvious.

Repeated observations indicated that rats seized by lithium and pilocarpine but then injected with ketamine did not display a subsequent history of epileptic seizures, continued to gain weight, and remained very healthy despite the severe multifocal brain damage as demonstrated by light microscopy (Vaillancourt & Persinger, 2001). Rats given our typical treatment, acepromazine, after the induction of the seizures, do not gain weight and display premature aging as defined by the earlier onset of yellowing of fur, odiferous secretions, and weight loss. The present experiment was designed to test the hypothesis that the process of aging, as indicated by old rats, would qualitatively indicate the consequences of changing the brain matrix during young adulthood.

Twelve male Wistar rats obtained from Charles River Breeders (Quebec) were employed as subjects. When the rats were about 90 days of age, eight had been injected with lithium (3 mEq/kg) and 4 hr. later with pilocarpine (30 mg/kg). Sixty min. after the injection of pilocarpine, four of these rats had been injected i.p. with 100 mg/kg of ketamine while another four rats were injected subcutaneously with 25 mg/kg of acepromazine. The seizures were induced on different days to minimize the confounds from any day-related effect. The rats were placed in single cages within which they lived for an additional 12 months. During this period their health was monitored by visual inspection, and food and water were available *ad libitum*. Each day an additional two food cubes were added to the cage; the occurrence of spontaneous seizures was recorded.

One year after the induction of the seizures, each rat was weighed, anesthetized with CO^2 gas, and decapitated. The brain was removed, weigh-

ed, and measured. The following organs were also measured to the nearest mg: thymus, thyroid, heart, spleen, pancreas, kidneys, adrenals, and testicles. Qualitative inspections were completed for the remaining organs including the deposition of adipose. One-way analysis of variance for the weights of the organs and the measurements of the brains were completed for the three groups. These and related analyses were completed by SPSS software.

There were statistically significant differences in body weight ($F_{2,11} = 18.56$, $p < .001$) among the three groups. *Post hoc* Tukey tests ($p < .01$) indicated that the ketamine groups were significantly heavier than the normal rats which were significantly heavier than the acepromazine-treated groups. The means and standard deviations (in parenthesis) for the three groups were 751 gm ($SD = 50$), 605 gm ($SD = 83$), and 468 gm ($SD = 58$), respectively. The ketamine-treated rats (all dfs = 2,11) had larger hearts ($F = 14.99$, $p < .001$), livers ($F = 5.62$, $p < .05$), and hypophyses ($F = 5.20$, $p < .05$) than the other two groups which did differ significantly from each other. For the ketamine group the means and standard deviations were 2.04 and .22 gm for the heart and 25.8 and 3.8 gm for the liver, and 0.18 and .003 gm for the hypophysis. For the other two groups (averaged), the means and standard deviations were 1.53 and .10 gm for the heart, 16.2 and 4.3 gm for the liver, and .014 and .001 gm for the hypophysis.

The means and standard deviations for the other organs whose weights did not differ significantly between the groups were: thymus .13 gm ($SD = .07$), thyroid .027 gm ($SD = .007$), spleen .128 gm ($SD = .58$), adrenals .06 gm ($SD = .017$), testicles 3.36 gm ($SD = 1.01$), pancreas 1.13 gm ($SD = .26$), kidneys 4.49 gm ($SD = .99$), and brain 2.09 gm ($SD = .13$). However, the widths of the cerebrums ($M = 16.1$, $SD = .10$ mm) for the ketamine-treated groups were significantly greater ($F_{15,10}$, $p < .001$) than for the other (averaged) two groups ($M = 15.1$ mm, $SD = .20$ mm), while the length of the cerebrum (grand $M = 15.5$, $SD = .46$) did not differ ($F = 0.48$, $p > .05$).

The most conspicuous qualitative observations were the youthful appearance of the seized rats which had been treated with ketamine (despite their actual age) and the nature of the adipose tissue responsible for their heavier body weights. The adipose tissue in these animals was densely packed in large, longitudinal packets, within the lower abdomen. This tissue was much whiter than the adipose tissue contained within either the normal rats or the seized rats which had received the acepromazine. The second qualitative feature was that the rats which had received the ketamine *never* displayed a single spontaneous seizure during daily observations.

These results suggest that rats into which ketamine had been injected shortly after the induction of seizures by lithium and pilocarpine showed weight gains over their lives which exceeded those of normal rats. Although rats which have received ketamine show comparable multifocal damage (Vail-

lancourt & Persinger, 2001) in almost all of the structures damaged when acepromazine was injected instead, the former group did not show the reduced width of the cerebrum. In previous studies employing rats which had been seized and received acepromazine, this reduction in width was associated with widening of the lateral ventricles (Persinger, Peredery, Desjardins, & Eastman, 1998).

Despite the qualitatively comparable microscopic damage within the rats which receive acepromazine or ketamine, the latter rats have not been observed to display overt seizures. We have hypothesized that the multifocal and graded loss of neuronal subpopulations generated by the lithium-pilocarpine-induced seizures allows a condition from which new functional organizations of the cerebrum can emerge. In contrast, large single lesions remove this potential because all of the cells within a given structure are destroyed.

We suggest that the brains of the rats which received the ketamine generated a different matrix that eliminated the occurrence of electrical seizures and normalized their capacities for conditioned taste aversion and for learning a complex radial maze (Stewart & Persinger, 2001; Vaillancourt & Persinger, 2001). This change may have also altered the processes that determine the amount and structure of adipose tissue. However, this manifestation became most evident during the later ontogeny of the rats. The extent to which environmental factors interacted with this process must still be explored.

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Accepted September 30, 2002.